Title

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Journal

CHEST Journal, 161(5)

ISSN

0012-3692

Authors

Teckchandani, Priyanka Heeru
Truong, Kimberly Kay
Zezoff, Danielle
et al.

Publication Date

2022-05-01

DOI

10.1016/j.chest.2021.11.012

Peer reviewed

CHEST

Transvenous Phrenic Nerve Stimulation for Central Sleep Apnea

Clinical and Billing Review

Priyanka Heeru Teckchandani, MD; Kimberly Kay Truong, MD; Danielle Zezoff, BS; William J. Healy, MD; and Rami N. Khayat, MD

Central sleep apnea (CSA) frequently coexists with heart failure and atrial fibrillation and contributes to cardiovascular disease progression and mortality. A transvenous phrenic nerve stimulation (TPNS) system has been approved for the first time by the Food and Drug Administration for the treatment of CSA. This system, remedē System (Zoll Medical, Inc.), is implanted during a minimally invasive outpatient procedure and has shown a favorable safety and efficacy profile. Currently, patient access to this therapy remains limited by the small number of specialized centers in the United States and the absence of a standard coverage process by insurers. Although a period of evaluation by insurers is expected for new therapies in their early stages, the impact on patients is particularly severe given the already limited treatment options for CSA. Implantation and management of this novel therapy require the establishment of a specialized multidisciplinary program as part of a sleep medicine practice and support from health care systems and hospitals. Several centers in the United States have been successful in building sustainable TPNS programs offering this novel therapy to their patients by navigating the current reimbursement environment. In this article, we review the background and efficacy data of TPNS and briefly address relevant aspects of the clinical activities involved in a TPNS program. The article presents the status of coverage and reimbursement for this novel therapy. We also discuss the current approach to obtaining reimbursement from third-party payors during this transitional period of evaluation by Medicare and other insurers.

CHEST 2022; 161(5):1330-1337

KEY WORDS: ambulatory payment classifications; central sleep apnea; CPT; Medicare; transvenous phrenic nerve stimulation

Central sleep apnea (CSA) is a type of sleep disordered breathing characterized by the periodic decrease (hypopneas) or absence (apneas) of respiratory drive. CSA events are distinguishable on polysomnography from OSA events by lack of respiratory effort during the event. CSA is most prevalent in patients with chronic heart failure (CHF).[1-3] In addition, CSA is encountered with higher frequency in patients with atrial fibrillation,

ABBREVIATIONS: AHI = apnea hypopnea index; ASV = adaptive servo ventilation; CAI = central apnea index; CHF = chronic heart failure; CPT = Current Procedural Terminology; CSA = central sleep apnea; FDA = Food and Drug Administration; ODI = oxygen desaturation index; PAP = positive airway pressure; TPNS = transvenous phrenic nerve stimulation

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (P. H. Teckchandani and R. N. Khayat), the School of Medicine (D. Zezoff), the UCI Sleep Disorders Center (R. N. Khayat), University of California, Irvine, Irvine; the Department of Pulmonary, Critical Care, and Sleep Medicine (K. K. Truong), Long Beach Veterans Affairs, Long Beach, CA; and the Division of Pulmonary, Critical Care, Sleep Medicine (W. J. Healy), Medical College of Georgia, Augusta University, Augusta, GA.

CORRESPONDENCE TO: Rami N. Khayat, MD; email: khayatr@hs.uci.edu

DOI: https://doi.org/10.1016/j.chest.2021.11.012

prior stroke, residence in high altitude, or chronic opioid use.[2] CSA causes cyclic hypoxia, oxidative stress, endothelial dysfunction, sleep fragmentation, and surges in BP, resulting in activation of the sympathetic system.[4-6] Consequently, increased arrhythmogenicity, hospital readmissions, and mortality all are observed in patients with CHF and CSA compared with those with CHF only.[7-9] Thus, patients with CSA potentially would stand to benefit from treatment, particularly those with underlying CHF.

A detailed discussion of pathophysiologic features of CSA is well beyond the scope of this review. However, we touch on the mechanism and treatment options as they pertain to the focus of this article. The reader is directed to a recently published review on this topic in this journal addressing the mechanistic considerations of treatment options for CSA.[5] We focus on transvenous phrenic nerve stimulation (TPNS) and appropriate coding and billing of the procedures associated with this treatment.

Overview of Current Treatment Options for CSA

Various positive airway pressure (PAP) devices have been used for treatment, but have demonstrated only partial efficacy or even, in one instance, increased mortality. Adaptive servo ventilation (ASV) was developed specifically for the treatment of CSA.[10] Early experience with ASV demonstrated superior efficacy in controlling CSA and improved clinical outcomes in some studies, predominantly from Japan.[11,12] More recently, The Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure, a multinational, multicenter randomized controlled trial, evaluated the effects of ASV and optimal medical management compared with medical management alone in symptomatic patients with heart failure with reduced ejection fraction and predominant CSA. This study reported increased mortality in the ASV group, which resulted in a black box warning for ASV therapy in patients with HrEF.[13] Given that the vast majority of patients with CSA also have underlying heart failure with reduced ejection fraction, an immediate gap in treatment options for patients with CHF and CSA ensued. Other treatments evaluated for CSA include acetazolamide and nocturnal supplemental oxygen.[5] These treatments have not been studied sufficiently in adequately powered long-term trials thus far and are not part of the standard approach for the treatment of CSA. It is important to note that no therapy, including TPNS, has demonstrated improvement in hospitalization or mortality in large, randomized studies.

Shortly after the publication of The Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure, the TPNS device remedē System (Zoll Medical, Inc.) was approved by the Food and Drug Administration (FDA) for the treatment of CSA in all clinical settings in 2017, including CHF, making it the only FDA-approved treatment for CSA in patients with ejection fractions of $< 45\%$.

Diaphragmatic pacing has been available for management of chronic respiratory failure in patients with neuromuscular disease and central alveolar hypoventilation syndrome.[14] The TPNS remedē System differs from these systems in that it is implanted via a minimally invasive transvenous approach, and it targets the pacing of only one hemidiaphragm. The device is implanted by a trained cardiologist (often an electrophysiologist) under moderate sedation, providing a clear advantage over general anesthesia because these patients often have serious comorbidities such as CHF and stroke. Because of the novelty of the interventions and its short time in clinical practice, no mechanistic studies are available yet that address the pathophysiologic pathways of CSA that TPNS targets. Although available studies enable some understanding of the pathways of action, it is notable that such mechanistic studies will be complicated by gaps in our understanding of the pathophysiology of CSA. Notably, we did not have adequate understanding of the mechanisms of action of other therapeutic interventions that have been used widely for CSA (eg, CPAP and ASV) as their adoption was increasing.

Overview of Safety and Efficacy of TPNS

TPNS has been shown to treat moderate to severe CSA in adults safely and effectively. Notably, most studies of TPNS included patients with concomitant cardiac devices. Results demonstrated reduction in apnea hypopnea index (AHI), central apnea index (CAI), oxygen desaturation index (ODI), and arousal index.[15-19] Initially, a pilot study demonstrated sustained improvement at 12 months in the AHI and sleep efficiency. A number of patients required lead repositioning, which resulted in a redesign of the left pericardiophrenic lead and the subsequent pivotal trial of the remedē System.[17,20] The FDA randomized approval study included patients with demonstrated moderate to severe CSA based on in-laboratory polysomnography scored by a blinded core laboratory.[18] Polysomnography inclusion criteria included: $\geq$ 4 h of

recording time with 2 h of sleep, AHI of ≥ 20 events/h, more central apneas than obstructive apneas, at least 30 central apneas, and no more than 20% of all events being obstructive apnea. In this trial, hypopneas were not classified as central or obstructive. Important exclusion criteria included CSA resulting from pain medications, recent strokes, severe COPD, and pacemaker dependence. All 151 patients underwent a TPNS device implant procedure and were randomized at the time of implantation attempt to either active TPNS therapy or control (therapy remained inactive for the first 6 months). The primary end point was ≥ 50% reduction in AHI at 6 months. The safety end points were device-, procedure-, and therapy-related serious adverse events through 12 months. The treatment group achieved a 50% reduction in AHI approximately 41% more than the control group ($P < .0001$).[18] At 12 months, 91% of patients were free of serious procedure-, device-, and therapy-related adverse events, which is similar to other transvenous devices such as implantable cardiac defibrillators. Additionally, the study met all seven prespecified secondary end points, including improvements in AHI, CAI, arousal index, ODI 4%, patient global assessment, Epworth sleepiness scale (all $P < .001$), and percent of sleep time in rapid eye movement sleep ($P = .0244$).

After the trial, TPNS therapy was activated in the control group after the 6-month efficacy end point, and patients continued to be followed up for up to 5 years. Data analyzed to date have demonstrated sustained improvements in AHI, CAI, and ODI 4%.[21] Recently, the 5-year data were published and demonstrated sustained improvements in AHI (median residual, 17 events/h; baseline, 46 events/h), CAI (median residual, 1 event/h; baseline, 23 events/h), and ODI 4% (median residual, 15 events/h; baseline, 39 events/h). Of note, in-laboratory polysomnography demonstrated sustained improvement of arousals and sleep quality at the 5-year mark. Safety persistently was demonstrated through 5 years with 86% freedom from serious related adverse events, which is similar to that of implantable cardiac devices.[21] A separate analysis demonstrated a significant reduction in the hypoxemic burden in the treatment group compared with control group. The median change from baseline was −16 min [95% CI, −44 to 0] in the treatment arm and +1 min [95% CI, −14 to 16] in the control group ($P < .001$).[22] Subgroup analysis did not identify predictors of nonresponse. Importantly, the FDA reviewed all available data again after the 5-year data were reported and confirmed approval in adult patients with moderate to severe CSA regardless of cause or ejection fraction.

One subgroup analysis was carried out in the 64% of patients with CHF.[15] Patients with CHF showed similar improvements in sleep metrics and quality of life. In addition, improvements were noted in ejection fraction and left ventricular dimension at 12 months compared with baseline in patients with known left ventricular dysfunction ($P < .05$). Minnesota Living with Heart Failure scores improved by 6.8 points ($P < .01$). Although sample sizes were small, the rate of hospitalization resulting from CHF at 6 months showed evidence of being lower in the treatment group ($P = .065$). An additional independent study of 24 patients with CHF demonstrated an improvement in 6-min walk distance in a hallway from 369.5 ± 163.5 m at baseline to 410 ± 169.7 m at the 6-month follow-up with TPNS treatment ($P = .035$).[23]

Patient Identification and Candidate Selection

Patients with CSA do not demonstrate typical symptoms.[15] They often are identified during work-up for fatigue and poor functional status among patients with CHF. Patients may report sleepiness, insomnia, or fragmented sleep. Diagnosis of CSA requires nocturnal polysomnography and accurate detection of flow, measurement of oxyhemoglobin saturation, and detection of respiratory effort. Given that the treatment effect of TPNS is noted almost exclusively on central events, ideal candidates for the implant would be similar to those enrolled in the pivotal trial, with most of their baseline events being central in the cause. The pivotal trial for the remedē System enrolled patients who had a CAI alone exceeding 50% of the total AHI.[18]

Therapy Activation and Follow-up

Figure 1 is a schema describing the care sequence of a typical patient who undergoes implantation with the remedē System. The first routine visit after implantation occurs at 4 to 6 weeks after the procedure. During the time between implantation and this visit, the device collects data on the patient's respiration and sleeping pattern. These data then are used to program the time at which therapy is started and stopped, as well as the common sleeping position of the patient. During this visit, therapy is activated along with patient training on breathing with the device. In most patients, programming is carried out with a stepwise increase in output starting with a lower level of stimulation that increases automatically over 6 weeks until the next office visit. After the device

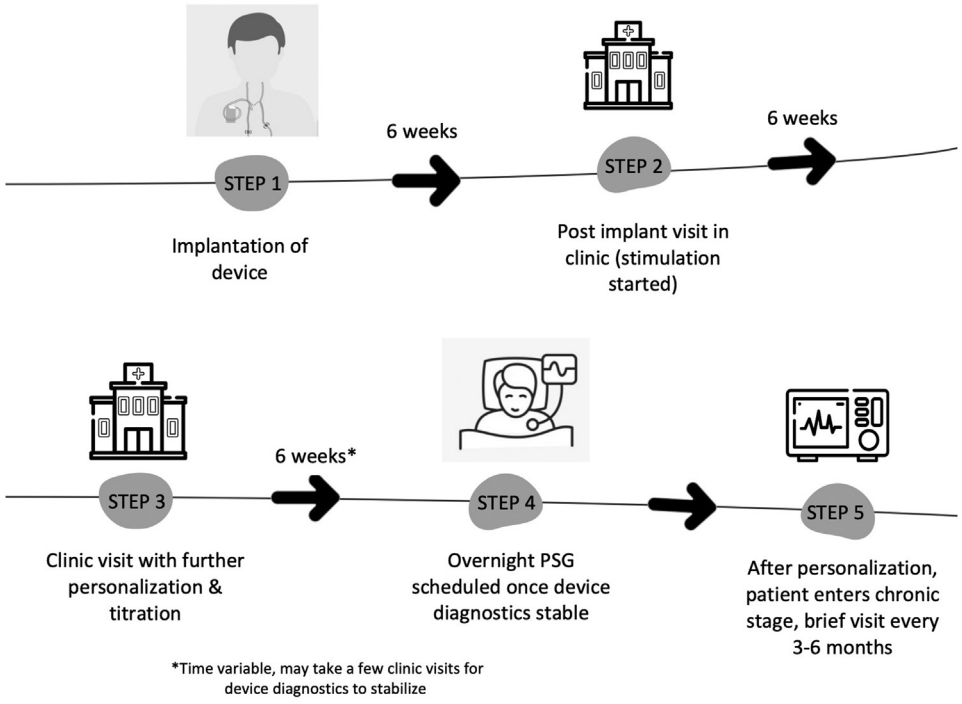

Figure 1 – *Diagram depicting the typical management of transvenous phrenic nerve stimulation in a patient with central sleep apnea. PSG = polysomnography.*

diagnostics are stable, the patient is scheduled for polysomnography. During polysomnography, final personalization programming is completed. After personalization is complete and efficacy is verified, the patient enters the chronic follow-up state and is seen for a brief visit every 3 to 6 months to check device function and battery levels. Because clinical status can affect CSA, it is recommended that the patient have an office visit after any cardiac-related hospitalization.

Reimbursement

Similar to other procedures and activities, reimbursement requires three components: coding, payment, and coverage. If any one of these items is missing, the procedure or activity will not be reimbursed. We discuss each of these components, with added focus on the on the role of the sleep center.

Coding and Billing

With all newly approved therapies, a period of evaluation occurs during which insurers consider the degree of use and impact of the technology before finalizing reimbursement. Because TPNS is a relatively new treatment, it remains under evaluation by insurers. However, its growing use likely soon will reach the level that requires payors to consider a standardized approach to reimbursement. Nevertheless, implantation of TPNS is performed currently in several centers throughout the country with successful reimbursement to the institution, especially in the cases of Medicare beneficiaries.

Initial evaluation of patients under consideration for TPNS use normal office visit Current Procedural Terminology (CPT) codes 99203 through 99205 or new outpatient consultation codes 99243 through 99245. Generally, in-laboratory polysomnography (code 95810) is used for patients with significant cardiovascular disease or comorbidities that raise suspicion for CSA or for a patient with known CSA who is referred to the sleep center for consideration of TPNS. Billing for professional fees of the physician to interpret the in-laboratory polysomnography is obtained by applying the 26 modifiers to the previously discussed codes. Follow-up visits to review polysomnography data and discuss the benefits and risks of TPNS are covered by codes 99213 through 99215, depending on medical complexity and time of the encounter. Code G2212 may be required to obtain reimbursement for prolonged periods of service spent by 15-min increments more than the time reimbursed by the primary visit codes.

When referring a patient for TPNS implantation, it is important to document the diagnosis of CSA (International Classification of Diseases, 10th Revision, code G47.31) in detail, including the overall AHI, CAI,

TABLE 1] Recommended Codes for Central Sleep Apnea

Description	ICD-9 Codes	ICD-10 Codes
Primary central sleep apnea	327.21, primary central sleep apnea	G47.31, primary central sleep apnea
Central sleep apnea with Cheyne-Stokes breathing	786.04, Cheyne-Stokes respiration	R06.3, periodic breathing
Central sleep apnea resulting from medical or neurologic condition without Cheyne-Stokes breathing	327.27, central sleep apnea in conditions classified elsewhere	G47.37, central sleep apnea in conditions classified elsewhere
Central sleep apnea resulting from drug or substance	327.29, other organic sleep apnea	G47.39, other sleep apnea

ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, 10th Revision.

and percentage of central events. Documenting initial symptoms (eg, daytime sleepiness, fragmented sleep) and related comorbidities and the rationale for treatment also is important. It is also crucial to make a note of any failed therapies, including PAP failure, PAP intolerance, or contraindication to ASV.

TPNS has a family of unique codes for both the implantation of the system and follow-up. These codes are CPT category III codes, which means that they are temporary and will be tracked closely to understand the use of the codes nationally. Eventually, these codes will be finalized into CPT category I codes or retired from use if not used. As seen in Tables 1-4, most codes are for the implantation procedure itself and describe different procedures that may be completed. CPT code 0424T is the code used for the full implant of the system and would be used most commonly by the implanter. Healthcare Common Procedure Coding System code C1823 is used in addition to code 0424T to characterize the TPNS system and is eligible for additional payment from Centers for Medicare and Medicaid Services described in the next section. Additional CPT, International Classification of Diseases, 10th Revision, Procedure Coding System, and Healthcare Common Procedure Coding System codes are described in Tables 2, 3, and 4, respectively.

More pertinent to the practice of sleep medicine are codes used for programming and patient follow-up. As noted above, the system is activated in the office at 4 to 6 weeks after implantation. Two unique office codes are available for the system: 0434T and 0435T. CPT code 0435T is used when programming changes, including therapy activation, are completed. CPT code 0434T is used when only an interrogation of the system is completed. Typically, polysomnography is completed at 12 to 24 weeks after therapy activation to optimize programming. Code 0436T is used to document programming changes completed during a sleep study.

Payment

The Centers for Medicare and Medicaid Services assign payment for each code depending on the setting of the services performed. TPNS typically is performed in an outpatient setting, and these codes are mapped to categories called ambulatory payment classifications so that similar services are paid in a similar manner. Occasionally, promising novel technologies that can demonstrate a substantial clinical improvement over existing therapies are granted additional payment for Medicare beneficiaries when the ambulatory payment classification is not sufficient to cover the procedure and technology, which is the case with TPNS. The payment program for therapies in the outpatient setting is called the transitional pass-through payment and essentially covers the cost of the technology separate from the procedure for several years until a final ambulatory payment classification amount is determined. The Healthcare Common Procedure Coding System (HCPCS) code C1823 must be used in addition to the CPT code 0424T to receive the additional transitional pass-through payment from Medicare.

Physician payment is separate from the hospital payment for the device or activity. Given the category III CPT code, no relative value units are established, and a description of the activity is needed when submitting for payment. Usually, a description of how the physician work is similar to other established activities is used, which is commonly called a "crosswalk." Therefore, for implantation (and in rare instances, for device removal), the physician is paid for the procedure at individual payer discretion on a case-by-case basis. Physicians establish their own charges and submit billing for the procedure based on charges for similar procedures they perform.

After final CPT category I codes are established for TPNS, a questionnaire is sent to the physicians performing these activities to establish relative value units. Until then, clear documentation of the time and

TABLE 2] Hospital Outpatient Procedure Reporting[25]

CPT Code	Description	OPPS APC	OPPS Status Indicator	2021 Medicare National Average Payment[15]
Insertion/replacement				
0424T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)	5465	J1	$29,444.52
0425T	Sensing lead only	5463	J1	$11,236.21
0426T	Stimulation lead only	5463	J1	$11,236.21
0427T	Pulse generator only	5465	J1	$29,444.52
Programming				
0434T	Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea	5742	S	$100.31
0435T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session	5742	S	$100.31
0436T	During sleep session	5724	S	$919.82

Hospitals use Healthcare Common Procedure Coding System (HCPCS) level I (eg, CPT) and HCPCS level II codes to report hospital outpatient services. Medicare Payment Status Indicators under OPSS, APC, and national average payments are provided for commonly reported remedē System procedures. CPT codes are provided and maintained by the American Medical Association.[25] APC = ambulatory payment classifications; CPT = Current Procedural Terminology; OPSS = Outpatient Prospective Payment System.

skill level of work are needed when submitting a claim for physician payment.

Coverage

Although the Centers for Medicare and Medicaid Services has recognized TPNS for a special payment program, coverage is left to the regional Medicare contractors given that no National Coverage Decision exists. Currently, Medicare has provided coverage for many patients when the therapy is determined to be medically necessary, but it is important to check with the local Medicare provider. Private insurers, including Medicare Advantage programs, often use a prior authorization process to determine coverage in advance of the procedure and accordingly to the manufacturer a high majority of the cases submitted are approved.

Medical necessity for TPNS should be stated explicitly in medical records. Insurers may request medical records for determination of medication need. When medical records are requested, letters of support often are useful. When referring a patient for TPNS implantation, it is important to document the diagnosis of CSA in detail, including overall AHI, CAI, and percentage of central events. Documenting initial symptoms (eg, daytime sleepiness, fragmented sleep) and related comorbidities and the rationale for treatment also is important. It is also crucial to make a note of any failed therapies, including PAP failure, PAP intolerance, or contraindication to ASV. The insurance reviewer may not have a background in sleep and may not understand the difference between CSA and OSA or that the treatments may differ. They also may not understand the need to treat after the disappointing results of the SERVE-HF trial. Thus, it is very important to demonstrate clearly in the note that the patient has CSA, not OSA. Documentation also should describe any relevant comorbidities that may be

TABLE 3] Hospital Inpatient The International Classification of Diseases, 10th Revision, Procedure Coding System (ICD-10-PCS) Codes[26]

ICD-10-PCS Code	Description
0JH60DZ	Insertion of multiple array stimulator generator into chest subcutaneous tissue
05H33MZ	Insertion of neurostimulator lead into right innominate (brachiocephalic) vein
05H43MZ	Insertion of neurostimulator lead into left innominate (brachiocephalic) vein
05H03MZ	Insertion of neurostimulator lead into azygos vein

Medicare hospital inpatient cases involving the use of the remedē System are eligible for new technology add-on payment. These cases should be identified with ICD-10-PCS codes 0JH60DZ and 05H33MZ in combination with either 05H43MZ or 05H03MZ.[26]

TABLE 4] Healthcare Common Procedure Coding System (HCPCS) Level II Device Descriptions[25]

HCPCS Code	HCPCS Long Description[22]
C1767	Generator, neurostimulator (implantable), non-rechargeable
C1778	Lead, neurostimulator (implantable)
C1787	Patient programmer, neurostimulator
C1823	Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads
C1887	Catheter, guiding
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only

Medicare hospital outpatient cases involving the use of the remedē System are eligible for transitional pass-through payment. These cases should identify the remedē System leads and implantable pulse generator with the Healthcare Common Procedure Coding System (HCPCS) code C1823 to be eligible for transitional pass-through payment.

worsened by the disease, including CHF, atrial fibrillation, and risk of stroke. It is helpful to document the clinical rationale for the decision to implant the TPNS, that is, explaining why the TPNS is the best or only available treatment option. Examples include: (1) ASV was contraindicated because patient had reduced ejection fraction; (2) the patient was unable to tolerate PAP therapies; (3) the patient attempted PAP therapy, but symptoms did not improve; and (4) the physician perceived a mortality risk for PAP therapy. After TPNS implantation is covered by insurance, office visits and programming changes typically are covered, but may still require a prior authorization based on the insurance company.

Significant parallels exist between the broader acceptance and availability of TPNS and its CPT codes with the evolution of recently introduced novel therapies and diagnostics such as fractional exhaled nitric oxide, bronchial thermoplasty, and hypoglossal nerve stimulation. These procedures began as CPT category III codes of emerging technologies or services. At this level, often noncoverage policies exist, and the corresponding CPT codes may be listed as experimental or investigational. As clinical evidence and therapy adoption increase, codes become CPT category I codes that often are better recognized by both private and public insurance plans across the United States. In the example of bronchial thermoplasty, the procedure was approved by the FDA in 2010. Professional organizations, specifically the American College of Chest Physicians and American Thoracic Society, supported the advancement to CPT category I, which was implemented by the American Medical Association on January 1, 2013.[24] This type of progression is expected to occur with TNPS, albeit at a different pace.

Developing a TPNS Program in the Sleep Practice

TPNS has gained wide acceptance because of the published safety and efficacy data and the lack of sufficiently acceptable alternative therapies. As such, comprehensive sleep medicine programs increasingly are seeking to provide this service. Developing a program to incorporate TPNS requires strong interdisciplinary partnerships, especially between sleep medicine and cardiology. As mentioned, most patients with CSA have cardiovascular issues such as CHF or atrial fibrillation. Working with the cardiology group to identify patients with sleep disorders is important, especially because symptoms of fatigue and sleepiness often are attributed mistakenly to the underlying cardiac disease. Additionally, as above, the device is implanted by an electrophysiologist experienced in implanting cardiac devices. In the early developmental stages of a TPNS program, this process can be aided by a program coordinator to assist with patient and staff education, patient screening, scheduling, interdisciplinary communication, and patient flow. Additional care providers, such as nurse practitioners, physician assistants, sleep technicians, cardiac device nurses, and schedulers, should receive education about TPNS and the device implantation procedure.

Conclusions

CSA is found commonly in patients with advanced cardiovascular disease and often is underrecognized and undertreated. Most available therapies thus far have been relatively ineffective, contraindicated, insufficiently studied, or not well-tolerated. TPNS was introduced recently and is currently the only FDA-approved therapy for CSA. TPNS shares features with hypoglossal

nerve stimulation, which is used for the treatment of OSA. Both therapies require an invasive implantation procedure and a specialized program to activate, optimize, and monitor the therapy in the long term. TPNS is relatively less invasive, however, because the device is implanted in a catheterization or electrophysiology laboratory. TPNS programs are starting to appear around the country and increasingly are viewed as a necessary component of a comprehensive sleep practice. Further growth and availability of this therapy to patients with CSA currently are impeded by the absence of full approval by third-party payors. Development of a program to administer and manage TPNS requires a multidisciplinary, integrative approach with involvement of a health care system and cardiology and sleep medicine departments. A well-conceived TPNS program can navigate the current reimbursement environment successfully using approaches similar to those used by other novel therapies in their earlier stages. These approaches have been described in detail and can ensure that a TPNS program can remain viable and can provide many patients with CSA with their only treatment option.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: R. N. K. received travel compensation for participation in an advisory board meeting for Respicardia, Inc., in 2019. None declared (P. H. T., K. K. T., D. Z., W. J. H.).

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